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Breast Cancer

Management of Unusual Histological Types of Breast Cancer

KAREN A. CADOO, ORLA MCARDLE, ANNE-MARIE O'SHEA, COLM P. POWER, BRYAN T. HENNESSY

Beaumont Hospital, Dublin, Ireland

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ABSTRACT

There is increased understanding of the heterogeneity of breast tumors, with greater emphasis now being placed on histological and molecular profiles and, in particular, their implications for prognosis and therapy. This review addresses breast cancers of unusual histological subtype with an approximate incidence ≤1%. Given the rarity of these tumors, the literature contains primarily case reports, small series, and population-based studies. Data are heterogeneous and almost entirely retrospective, frequently gathered over long time periods, in the context of changing pathological techniques and reporting. In addition, our understanding of the disease biology and therapeutic context has also evolved significantly over this time. There is often limited information about the specific therapies used and the rationale for choosing such an approach. Meaningful comparisons of treatment modalities are not feasible and it is not possible to define management guidelines. Instead, this review correlates the available information to give an impression of how each subgroup behaves—of the favored surgical technique, responses to therapy, and prognosis—as well as the emerging molecular data, highlighting new research areas for potential target in clinical trials. Each tumor subtype described represents a small but real cohort of patients with breast cancer, and although inferences may be made from this review, we are mindful of the paucity of data. The management of each patient must be considered in the context of their unique clinical presentation and correlated with the evidence-based principles that apply to more common breast cancer histologies. ***The Oncologist*** 2012;17:1135–1145

INTRODUCTION

There is increased understanding of the heterogeneity of breast tumors, with greater emphasis now placed on histological and molecular profiles, including their implications for prognosis and therapy (Table 1) [1–78]. This article addresses breast cancer with unusual histological subtypes but does not include other neoplasms that arise in the breast, for example, lymphoma, sarcoma, and phyllodes. To define unusual, a cutoff incidence of ~1% was applied, based primarily on the reported incidences in a recent Dutch population-based study [1].

This article reviews the available data on adenoid cystic carcinoma, apocrine carcinoma, cribriform carcinoma, metaplastic breast cancer (with particular emphasis on the squamous subtype), papillary cancer, and secretory breast cancer. Given the rarity of these tumors, the literature contains primarily case reports, small series, and population-based studies. Data are heterogeneous and almost entirely retrospective, frequently gathered over long time periods in the context of changing pathological techniques and reporting. The understanding of disease biology and the therapeutic context have also evolved, and there is limited information about the specific therapies used and the rationale for choosing such an approach. Meaningful comparisons of treatment modalities are not feasible; therefore, it is not possible to define management guidelines. Instead, this review correlates the available information to give an impression of how each subgroup behaves—of the favored surgical technique, responses to therapy, and prognosis—as well as the emerging molecular data, highlighting new research areas for potential targets in clinical trials. Although inferences can be made from this review, in the absence of more robust histologically specific data, the evidence-based principles used in the management of more common breast cancer histologies must apply.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) of the breast accounts for <0.1% of breast cancers [1–3]. It is histologically similar to ACC of the salivary glands [47] but confers a better prognosis

Correspondence: Karen Cadoo, M.B., B.Ch., B.A.O., Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, 300 East 66th Street, New York, New York 10065, USA. Telephone: 646-888-4551; Fax: 646-888-4555; e-mail: cadook@yahoo.com Received March 25, 2012; accepted for publication June 12, 2012; first published online in ***The Oncologist*** *Express* on July 23, 2012. 1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0134

Table 1. Incidence, presentation, imaging, and pathological data of unusual histological types of breast cancer, with text focusing on management approaches, prognosis, and molecular data where available

Subtype	Adenoid cystic carcinoma	Apocrine carcinoma	Cribriform carcinoma	MeBC	MeBC: squamous cell carcinoma subtype	Papillary cancer	Secretory breast cancer
Proportion of breast cancers	0.1% [1–3]	0.4% [4, 5]	0.1 %–0.6% [1, 6, 7]	0.2%–0.6% [1, 8–10]	<0.1% [11–13]	0.7% [1, 14, 15]	0.15% [16]
Male incidence	Case reports [2, 17–19] with aggressive disease in two cases [2, 19], an unremarkable clinical course in a third [18], and limited data in a series[17]	No male cases noted	Rare male cases have been reported [20]	No male cases noted	Only female cases [21]	3.5% of cases are male [22]	0.2% of male breast cancers [23]; occurs in both genders in children, but more common in girls [24, 25]
Age, yrs	Median, 58–66 [2, 3, 17, 26, 27]	Mean, 52–61 [4, 28, 29]	Median, 54–63 [1 ,6]	Median, 47–61 [1, 8–10, 30–32]	Mean, 54–64 [11, 13, 21, 33, 34]	Median, 65–70 [14, 15, 22, 35, 36]	Median, 25–40 [37–39]; 17 in males [23]
Clinical presentation	Palpable mass, often tender [2, 40]	Palpable mass [41]	Palpable mass; more recent series include screen detected cancers [6]	Tumors are large at presentation [8–10, 30–32], often present with a rapidly growing palpable mass [10, 30, 32, 42], bloody nipple discharge has been reported [32]	The majority present with a palpable mass [33] but may present with skin ulceration [21, 33] or an abscess [21, 43]	Bloody nipple discharge, palpable mass, or on screening mammography [14, 15, 36]	Palpable mass [23, 38, 39, 44, 45] that is frequently subareolar [23, 44, 45]; often present for long period prior to presentation [16, 44, 23, 37] with a mean diagnostic lag >3 yrs, suggesting that this is an indolent disease [37]. May be screen detected [39], however, patients often present outside the age group involved in screening [46]
Pathological features	Morphologically similar to adenoid cystic carcinoma of salivary glands [47]; composed of a biphasic population of cells—epithelial cells with varying glandular, squamous, and sebaceous differentiation, mixed with basaloid or myoepithelial cells; neoplastic cells are arranged in trabecular tubular, cribriform, and solid patterns; tumor contains true lumina lined by epithelial cells and pseudolumina lined by basaloid cells with myxoid and eosinophilic basement membrane material, imparting a cylindromatous appearance in some cases [48, 49]	May arise from pre-existing benign apocrine epithelium [50]; microscopically cells have abundant foamy to granular eosinophilic cytoplasm and round nuclei with prominent nucleoli [4]	Pure invasive cribriform carcinoma implies 90% of the tumor has a cribriform architecture [6] without other infiltrating tumor components [51]; in mixed cribriform carcinoma, up to 50% of the tumor is composed of another type of invasive carcinoma [52] tumor cells are arranged in irregular cribriform islands, which can resemble cribriform DCIS [6] but without the smooth contour and myoepithelial layer associated with in situ disease [52]; there may also be associated foci of DCIS, usually of cribriform histology [7]	Heterogeneous group, classified into broad subtypes [53]. I. Purely epithelial: squamous (large cell keratinizing, spindle cell, acantholytic); adenocarcinoma with spindle cell differentiation; adenosquamous, including mucoepidermoid. II. Mixed epithelial and mesenchymal; carcinoma with chrondroid metaplasia; carcinoma with osseous metaplasia; carcinosarcoma	>90% of malignant cells are of the squamous type and the tumor does not originate from nipple or skin or other sites of primary squamous cell carcinoma [54]	Encapsulated papillary carcinoma is a solitary cystic lesion with a fibrous capsule; myoepithelial cells are usually absent both within and around the lesions. Solid papillary carcinoma is composed of circumscribed nodules of epithelial cells, which are ovoid or spindle shaped with low nuclear grade, surrounding fibrovascular cores. Pure invasive papillary carcinoma is rare, controversial, and difficult to diagnosis histologically (see discussion in text)	Well-circumscribed mass, but margins may be infiltrative [37]; distinctive microscopic appearance [44]; cells contain abundant granular eosinophilic [38] and vacuolated cytoplasm and are arranged in tubular, microcystic, and solid patterns with eosinophilic periodic acid Schiff positive, diastase-resistant and α-lactalbumin-positive secretory material [37. 39]

(continued)

[18]. The median age at presentation is 58–66 years [2, 3, 17, 26, 27], and the majority of cases are female; however, male patients have been reported [2, 17, 19]. More than 85% of patients are white; the remainder is equally split between black and unspecified race [17, 26]. The median tumor size is 1.8–2.2 cm [2, 3, 17, 40], with lymph node involvement occurring in <5% of cases [3, 17, 26, 40, 55]. The significance of lymph node involvement is not clear [2, 3] because distant metastatic disease has been reported without axillary involvement [3, 18, 47]. ACCs of the breast have low proliferative activity [3], and <2% are metastatic at presentation [3, 17, 26, 40]. They are estrogen receptor $(ER)^+$ in 0%–46% of cases [3, 17, 18, 40, 55] and progesterone receptor $(PR)^+$ in 0%–36% of cases [3, 17, 40, 55]. Series that have addressed human epidermal growth factor receptor 2 (HER-2) status found tumors to be universally negative [40, 55].

Varying rates of mastectomy and breast-conserving surgery are reported [2, 3, 17, 18, 26, 40, 55], with a high positive margin rate (33%–86%) after breast-conserving surgery [18, 27, 40]. This is not surprising given the propensity of these tu-

Table 1. (Continued)

Subtype	Adenoid cystic carcinoma	Apocrine carcinoma	Cribriform carcinoma	MeBC	MeBC: squamous cell carcinoma subtype	Papillary cancer	Secretory breast cancer
Imaging	Mammographically presents as an irregular mass with indistinct margins, subtle architectural distortion, or a developing assymetric density; it is not associated with calcifications [55]; on ultrasound, a mass may be visible with hypoechoic or heterogeneous echotexture [40] with poorly defined margins [55]; seen on MRI as lobulated masses with irregular margins and variable T2-weighted findings depending on the extent of solid component [55]	Mammographically similar to invasive ductal cancer [50]	Mammographically occult in 4/8 cases in a small series [6]; tumors that were visible presented as large spiculated masses, some had associated punctate calcifications; of the women who presented with a mass but normal mammography, all had abnormal ultrasounds [6]; on ultrasond, cribrifrom cancers present as inhomogeneous, ill-defined, hypoechoic masses [6, 56]	Mammographically evident as highly dense masses [32, 42] without microcalcifications, architectural distortion, or prominent spiculations [32] in one series, although a second, larger but older, series found a minority had microcalcifications and a large number had architectural distortion [42]; margins may be well circumscribed, microlobulated, ill defined, or partially obscured by the surrounding breast parenchyma [32, 42]; lesions with very well-defined margins may be mistaken for benign tumors [32]; on ultrasound, masses may be homogeneous or heterogeneous, with complex solid and cystic components [32, 42]	Mammographically, no specific features [21, 33] but do have suspicious appearance with an irregular lobulated mass and poorly defined borders, usually without microcalcification [57]; ultrasound may demonstrate solid hypoechogenic masses with complex cystic components [58]; MRI may detect a circumscribed mass with necrotic center [34]	It is difficult to distinguish benign papillomas from papillary carcinoma by imaging alone [59]; mammographically, may present as a round, oval, or lobulated circumscribed mass or clusters of masses that may have associated microcalcifications [59, 60]; ultrasound is more sensitive than mammogram in detecting papillary lesions [61], visible as single or multiple circumscribed solid or complex cystic masses, which can bleed centrally [59, 60]; contrast-enhanced MRI may demonstrate significant enhancement of cyst walls, septations, and mural nodules [60]	Mammographically, presented with circumscribed isodense nodules, without microcalcification or architectural distortion in one series [39]; however, microcalcifications were identified in another series [38]; ultrasound may demonstrate a hypoechoic or isoechoic round or oval mass with well-circumscribed or microlobulated margins and a predominantly homogeneous texture [39]
Differential diagnosis	(a) Invasive cribriform carcinoma, (b) cribriform DCIS, (c) collagenous spherulosis, (d) for basaloid variant: high-grade IDC, small cell carcinoma, solid papillary carcinoma, and lymphoma; an IHC panel including hormone receptors, CK7, myoepithelial markers, and CD117 (with or without neuroendocrine and lymphoid markers) is helpful	(a) Atypical apocrine proliferations involving sclerosing adenosis (myoepithelial IHC helpful); (b) secretory carcinoma	(a) Cribriform DCIS (myoepithelial layer present); (b) adenoid cystic carcinoma (usually $ER^{-}PR^{-}$); (c) neuroendocrine carcinoma (differentiated by appropriate IHC panel)	Depends on morphology: (a) predominantly spindle cell lesions: primary breast sarcoma, phyllodes tumor; broad IHC panel essential, should include both low and high molecular weight cytokeratins (e.g., AE1/3, Cam5.2, 34βE12, CK5/6 and CK7) as well as p63; (b) carcinomas with squamous cell features: metastatic squamous cell carcinoma, primary skin squamous cell carcinomas; thorough sampling of lesion is essential to identify small foci of IDC or DCIS, which would both support a diagnosis of MeBC	(a) Metastatic squamous cell carcinoma; (b) invasive squamous cell carcinoma arising in the overlying skin	(a) The differential diagnosis for encapsulated papillary carcinoma includes papillomas containing foci of DCIS and papillary ductal carcinoma in situ	(a) Apocrine carcinoma; (b) lobular carcinoma with signet ring cell differentiation; (c) acinic cell carcinoma; (d) glycogen- or lipid-rich carcinomas
Average size	1.8–2.2 cm [2, 3, 17, 40]	>2 cm [4, 29]	1.9 cm [6] to 3.1 cm [7]; the majority (52%) present with stage I disease [1]	70% have tumors >2 cm [8, 9, 30, 31]; the majority present with stage II disease [30]	Tumors are large, often >4 cm [21, 33]; ~50% have stage II disease at diagnosis [11]	>80% are stage I /II at presentation [1, 35]	Limited data; maximum tumor size reported is 16 cm [38]; older patients tend to present with larger tumors [44]; in a review of the literature [37] staging was available in only 24/121 cases, 6 had metastatic disease, the rest had predominantly stage I/II disease
Grade (Nottingham method [62])	Low (Ro method [47])	50%–56% grade II [4, 29]	Often grade I	High incidence of grade III [1, 8, 9, 30]	Most are grade III [11, 21]	40%–47% grade I, 40%–50% grade II [35, 63]	Grade I and II usually

(continued)

Table 1. (Continued)

Subtype	Adenoid cystic carcinoma	Apocrine carcinoma	Cribriform carcinoma	MeBC	MeBC: squamous cell carcinoma subtype	Papillary cancer	Secretory breast cancer
ER and PR status	ER^+, 0%–46% [3, 17, 18, 40, 55]; PR^+, 0%– 36% [3, 17, 40, 55]	ER^-PR^- [29, 50]	Usually ER^+ [51, 52, 56]; may be PR^+ [51, 56], 69% PR^+ in one series [51]	70%–100% ER^-PR^- [8, 10, 30, 31, 64–66]; often classified as a variant of triple-negative breast cancer despite its heterogeneity [9, 66]	>85% of patients are ER^-PR^- [11, 21, 67]	88% ER^+; 82% PR^+ [35]	Usually ER^-PR^- [37, 38, 45, 68]
HER-2 status	Limited data, but series that addressed HER-2 status found tumors to be negative [40, 55]	HER-2^+, 33%–54% [4, 29, 69, 70]	Two case reports tested for HER-2, both were negative [52, 56]	HER-2^- [10, 30, 31, 64–66]	Majority are HER-2^- [11]	Negative [71]	Predominantly HER-2^- [45, 68]
Proliferative activity	Low [3]	p53, 29%; bcl-2, 25%; MIB-1 index, 29% [29]	Low Ki 67 [56]	High Ki67 and p53 positivity [9, 30, 65, 72]	High Ki-67 proliferation in case reports [43, 58]	Likely low [1, 73]	Nuclear atypia and high mitotic index are not seen [37] and they demonstrate low Ki 67 [38, 68]
Lymph node status	<5% involved [3, 17, 26, 40, 55]; significance of nodal disease is not clear [2, 3]; distant metastases have been reported without axillary involvement [3, 18, 47] and there are questions about the the role of axillary sampling [3, 18, 74]	21%–26% involved [4, 29], although 51% in one series [28]	10% involved [7], usually <3 nodes involved [51]	Up to 78% node negative at presentation [8, 9, 30–32, 42]; however, despite this, there is greater potential for distant metastasis [30]; recurrence rates for node-negative MeBC are up to 60%, compared with 20% for IDCs of similar size [72]	Often node negative [33]; a review of the literature found that >70% of patients presenting with localized disease had no nodal involvement [21]; however, in one series [11] only 48% of patients were node negative	Low risk for node positivity, 3%–12% in one series [63]	Nodal involvement in 20%–30% [23, 24, 39, 75]
Proportion metastatic at presentation	<2% [3, 17, 26, 40]	None [4, 28, 29]	None [51]	4.6%–10% [8–10]	8%–10% [11, 34]	2.5% [14]	Not clear; in a review of the literature [37], staging available in only 24/121 cases, 6 had metastatic disease
Prognosis	Good, 85% to >90% [2, 3, 17, 18, 40, 55]; survival rates are similar to the general population[76]	Better than IDC, NST [28] in some series	5-yr relative survival risk of 104% [1]	Lower disease-free survival rate (41% versus 87%) and 5-yr survival rate (63% versus 92%) than with IDC of all subtypes [9]	Poorer than other breast cancer histologies [11, 33, 34]; 5-yr survival rate, 50%–67% [11, 21, 33]	Good [1, 22, 35]; >80% 5-yr survival rate [15, 22, 77]	Good [23, 37, 78]

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IHC, immunohistochemical; MeBC, metaplastic breast cancer; MRI, magnetic resonance imaging; NST, no special type; PR, progesterone receptor.

mors for perineural invasion as well as microscopic infiltration of adjacent tissue [18]. In addition, margins are poorly defined on imaging [55]. However, the impact on prognosis is questionable—despite positive margins in six of seven patients in one series, there was only one local recurrence, with no metastatic disease or deaths [40]. Similarly, another study ($n = 31$) reported three cases with positive margins but only one local recurrence, and all patients were alive without disease [18]. The prognostic significance of nodal disease [2, 3] and the role of axillary sampling [3, 18, 74] are also unclear because distant metastatic disease can occur without axillary involvement [3, 18, 47].

Coates et al. [26] demonstrated ($n = 376$) that postoperative radiation resulted in a superior survival outcome. They suggested that the benefit was primarily driven by the lumpectomy cohort because few patients had postmastectomy radiation. Perhaps the addition of radiation circumvents the issue of microscopic local infiltration and positive margins with breast-conserving surgery.

Some, but not all, women with breast ACC who are ER^+ receive adjuvant endocrine therapy. For example, in one series, six of 13 ER^+ patients received hormonal therapy. The rationale for choosing or withholding this therapy was not clear [3]. Small numbers received adjuvant chemotherapy [2, 3], but again the indication was not clear. The chemotherapy regimen and duration were not specified, nor were these patients separately reported in terms of outcome. The role of adjuvant systemic therapy, therefore, remains undefined.

These patients have a good prognosis overall. Local recurrence rates are low (3%–18% [3, 18, 40, 55]), and if local recurrence occurs, more than half of these patients can be cured with further surgery [3]. Distant metastases develop in ~10% of cases [2, 3, 18, 40, 55], and the survival rate is in the range of 85% to >90% (with a minimum of 5 years of follow-up) [3, 17, 18, 40, 55]. Extrapolating from ACC of the salivary glands, Ro et al. [47] (n = 12) stratified tumors into three grades based on the proportion of solid growth (grade I, no solid component; grade II, <30% solid; grade III, >30% solid) and suggested

that those with a greater solid component were associated with a poorer prognosis. However, another larger series ($n = 31$) found that histological grading was not prognostically useful [18].

These are good prognosis cancers and it may be reasonable to infer that breast-conserving surgery is possible with adjuvant radiation. Lymph node sampling may not be necessary given the low rates of lymph node involvement and the possibility of distant metastasis unrelated to nodal involvement [2, 18]. Consideration of adjuvant systemic therapy should be mindful of the low proliferative activity of this tumor [3] and the paucity of available data.

Apocrine Carcinoma

The definition of invasive apocrine carcinoma as a separate entity is controversial and it is often considered a variant of invasive ductal carcinoma (IDC), no special type (NST) [79]. O'Malley and Bane [79] cite two studies [41, 80] that compared invasive apocrine carcinomas with matched NST tumors and found no difference in survival outcomes. Those studies concluded that apocrine carcinoma is not a clinically distinct subtype. However, it has been described since 1916 [28], and more recently Japaze et al. [28] argued that pure invasive apocrine carcinoma is a distinct disease, which when strictly defined by their criteria may be less aggressive than IDC, NST.

Apocrine carcinoma accounts for ~0.4% [4, 5] of invasive breast tumors. The mean age at presentation is 52–61 years [4, 28, 29], with only female cases noted. Apocrine carcinoma has a mean tumor size >2 cm [4, 29] and is associated with a lower frequency of axillary nodal involvement, less lymphovascular involvement [4, 29], and a lower histological grade [4, 28] than IDC, NST in some studies. Case series describe ER^+ patients; however, patients are more likely to be ER^-PR^- [29, 50]. Reported incidences of HER-2 overexpression are in the range of 33%–54% [4, 29, 69, 70].

In one series that looked at stage I/ II disease ($n = 37$) [28], 35% of patients had breast-conserving surgery, 92% had lymph node dissection, 46% had radiation, and 95% received adjuvant therapy (chemotherapy or tamoxifen). This group compared the outcomes with those of matched IDC cases and found similar frequencies of lymph node involvement but fewer nodes involved (mean of three nodes for the apocrine group versus five nodes for the IDC group) and a better overall survival outcome with apocrine cancer [28]. None of the patients with apocrine carcinoma and a negative axilla had died, compared with four of 31 IDC patients with a negative axilla. Despite reports of HER-2 overexpression, there are no published reports describing the use of HER-2–targeting drugs.

Apocrine carcinomas are often ER^-PR^- and have been demonstrated to have greater androgen receptor (AR) expression [69, 70, 81, 82]. There is emerging recognition of the "molecular apocrine" subtype with this characteristic receptor profile. In these patients, androgen signaling may replace estrogen signaling as the driver of carcinogenesis and could represent a target for therapy [83]. Further, this molecular apocrine profile may identify a group with bigger tumors than those with classical apocrine histology [83]. Weigelt et al. [76] suggested that these cancers have heterogeneous gene-expression profiles, relevant to multiple molecular subtypes rather than representing a distinct entity. Vranic et al. [70] concurred that these are molecularly diverse cancers; however, they suggested that pure apocrine cancer, limited to a characteristic profile of ER^-PR^- and AR^+, defines a group that is either HER-2 overexpressing or triple negative, whereas apocrine-like tumors (which do not have the characteristic steroid receptor expression profile) are more likely to have a luminal phenotype, with consequent therapeutic implications.

In addition, the current methods measure antibodies to a full-length ER-α protein—ER-α66. However, a novel isoform, ER-α36, has been studied, and a high level of expression was noted in pure apocrine cancers along with high coexpression of epidermal growth factor receptor (EGFR) [69]. This ER-α36 expression may have prognostic significance; in addition, patients whose tumors coexpress ER-α66 and ER-α36 have been demonstrated to be resistant to tamoxifen [84].

Apocrine carcinoma is likely a distinct clinicopathological and molecular entity, separate from IDC, NST. It is probably best defined by an $ER^-PR^-AR^+$ profile as well as classical morphology. There are limited data regarding adjuvant therapy; however, it is worth considering this group independently as we try to exploit molecular targets and improve outcomes.

Cribriform Carcinoma

Invasive cribriform carcinoma was first described in detail by Page et al. [7] in 1983. However, the literature related to this disease is sparse, particularly in the last 10 years. They account for 0.1%–0.6% of breast cancers [1, 6, 7], with a median age at diagnosis of 54–63 years [1, 6]. Rare male cases have been reported [20]. Most patients present symptomatically with a mass, but more recent series include screen-detected cancers with a smaller average average size (1.9 cm) [6] than in earlier reports (3.1 cm) [7]. Lymph node involvement occurs in ~10% of cases [7] and the proliferative activity is low [56]. Tumors are usually ER^+ [51, 52, 56] and may be PR^+ [51, 56] (69% were PR^+ in one series [51]). Two case reports tested for HER-2 status and both were negative [52, 56].

A Dutch population study [1] reported that, in their cohort aged >70 years ($n = 21$), the majority had surgery only (57%). However, in the cohort of patients aged <70 years ($n = 42$), 74% received adjuvant radiation or systemic therapy or both. Information regarding the type of systemic therapy was not provided. However, patient outcome was excellent, with a survival time similar to that of women who did not have breast cancer [1]. This is in keeping with other studies that reported a favorable prognosis for patients with this breast cancer subtype [7, 20, 51, 85, 86].

CD44 is an extracellular transmembrane molecule with a variable domain (v2–v10) that has been implicated in the metastatic spread of cancer cells and may have value as a prognostic marker [87]. Saleh and Reno [87] looked at the expression levels of the CD44 v3, v4, and v6 isoforms in six cases of pure invasive cribriform cancer and compared them with those of other breast histologies. The majority (83.3%) of the cribriform cancers had extensive expression of CD44 v3 whereas

>85% of the mucinous, papillary, ductal, and lobular cancers did not. There was no association between histological subtype and CD44 v4 or v6 expression. They suggested that extensive expression of CD44 v3 may reflect a good rather than bad prognostic marker, and they reference Bassarova et al. [88], who found that strong expression of CD44 v3 was not associated with metastasis. However, other studies suggest that expression of CD44 v3 is correlated with a higher tumor grade, lymph node involvement, and a poorer survival outcome [87].

Cribriform carcinoma has an excellent prognosis in its pure form. In its mixed variant, it also has a good outcome but perhaps should be considered with more caution. The extent of surgery required and the roles of adjuvant radiation and systemic therapy are unclear. If CD44 v3 is validated as a favorable prognostic marker, perhaps its value would be in selecting those who do not have extensive expression as a higher risk group. This could be used to guide treatment decisions, saving those who are in a good prognostic group from unnecessary therapy.

Metaplastic Breast Cancer

Metaplastic breast cancers (MeBCs) represent a heterogeneous group of tumors classified into broad subtypes based on their phenotypic appearance [53], described by the World Health Organization as a mix of adenocarcinoma with dominant areas of spindle cell, squamous, and mesenchymal differentiation [53]. MeBCs are classified as either purely epithelial (including squamous cell carcinoma, adenocarcinoma with spindle differentiation, and adenosquamous carcinoma) or mixed epithelial and mesenchymal (including carcinoma with chrondroid metaplasia, carcinoma with osseous metaplasia, and carcinosarcoma) [53]. In addition, a metaplastic carcinoma with osteoclast-like giant cells has been described [30].

The incidence of MeBC is in the range of 0.2%–0.6% [1, 8–10], with a median age at presentation of 47–61 years [1, 8–10, 30–32]. There are no male cases noted. Tumors are large, with 70% of patients having tumors >2 cm at diagnosis [8, 9, 30, 31]. The majority of MeBCs are node negative at presentation [8, 9, 30–32, 42]; however, despite this, there is a greater potential for distant metastasis [30]. Patients with MeBC present with de novo metastatic disease in 4.6%–10% of cases [8–10]. MeBC demonstrates high Ki67 and p53 positivity [9, 30, 65, 72] and tumors are usually ER^-PR^- [8, 10, 30, 31, 64–66] and $HER\text{-}2^-$ [10, 30, 31, 64–66]. MeBC is often classified as a variant of triple-negative breast cancer, despite its heterogeneity, but it has been demonstrated to confer a poorer prognosis than with triple-negative cancers of invasive ductal histology [9].

A large database study ($n = 892$) [8] found that 56% of patients with MeBC, compared with 38% with IDC, had a mastectomy. However, when the larger size of the MeBC was taken into account, the rates of breast-conserving surgery and mastectomy were similar. Forty-three percent of MeBC cases and 52% of patients with IDC had adjuvant radiation, but a significantly greater proportion of patients with MeBC received adjuvant chemotherapy (53.4% versus 42.1%; $p = .001$). The small number of patients with MeBCs that were ER^+ received hormonal therapy (6.4%). These findings were replicated by a Korean database study ($n = 35$) that found that patients with MeBC had larger tumors, had less nodal involvement, were more likely to have a mastectomy and be treated with chemotherapy, but were less likely to have adjuvant radiation than patients with IDC [9].

A Japanese study [31] compared cases of IDC ($n = 6{,}137$), lobular breast cancer ($n = 301$), and MeBC ($n = 46$). There were significantly lower frequencies of lymph node involvement and administration of neoadjuvant or adjuvant therapy in the MeBC group but a higher frequency of skin invasion than in patients with IDC. MeBC conferred a significantly higher hazard ratio for recurrence and tumor-related death than IDC, independent of nodal status. Factors associated with recurrence and death were patient age <39 years, neoadjuvant chemotherapy, the presence of skin invasion, a squamous cell component in lymph node metastases, and tumor stage. Factors associated with death were the grade of disease in lymph nodes, the presence of extranodal extension, and adenocarcinoma with spindle cell differentiation in lymph nodes [31].

Other studies support a poor prognosis [9, 10, 30] with MeBC, and local recurrences are frequent [10]. In patients with metastatic disease, the median survival time was 8 months from recurrence. Several retrospective studies [89, 90] found no survival advantage with adjuvant chemotherapy. Adjuvant radiation has been recommended [10], but the data are limited. It has been suggested that the lower rate of nodal involvement, particularly given the larger tumor sizes with MeBC than with IDC, points to different tumor biology for this disease [8].

Poor responses in the metastatic setting [10, 89] raise questions about the sensitivity of MeBC to conventional breast cancer chemotherapies [64, 91]. There is a predilection for local failure and pulmonary metastases, and it has been suggested that MeBC behaves like sarcoma [10]. Occasional responses have been seen with doxorubicin [10, 89], and there have been a number of cases reporting responses to ifosfamide-based regimens [92, 93].

MeBCs express some markers associated with basal cancers—EGFR, cytokeratin-5, and cytokeratin-6—however, their clinical features suggest that they represent a unique subtype [64]. This basal-like phenotype may account for their poorer prognosis and also may be associated with poorer responses to chemotherapy [66]. *EGFR* gene amplifications were demonstrated in 37 of 65 (57%) MeBC cases in one study, providing a rationale for investigating EGFR inhibitors as a treatment modality [66]. Reis-Filho et al. [91] suggested that MeBC with amplified *EGFR* may respond to tyrosine kinase inhibitors.

Hennessy et al. [64] applied an integrated genomic–proteomic approach to a group of MeBC patients ($n = 28$) with squamous and sarcomatoid metaplasia to investigate mechanisms of carcinogenesis and chemoresistance. They suggested that MeBC most closely resembles claudin-low triple-negative breast cancer with a loss of genes involved in cell–cell adhesion. They proposed that MeBC may arise from immature precursor cells and that enrichment for stem cell–like and epithelial–mesenchymal transition markers as well as activa-

tion of the phosphatidylinositol 3-kinase (PI3K)–Akt and mitogen-activated protein kinase (MAPK) pathways, frequently a result of *PI3KCA* mutations, may account for the aggressive phenotype and chemoresistance of this disease. Novel drugs that inhibit the PI3K–Akt and MAPK pathways may provide therapeutic potential.

MeBC is a heterogeneous disease that confers a poor prognosis. Mastectomy is used more commonly than breast-conserving surgery [10], and given the large median size of these tumors it may be the optimum approach. Data regarding adjuvant chemotherapy are not robust. However, poor responses to conventional chemotherapy in the metastatic setting [10, 89] and increasing understanding of the molecular mechanisms underlying this disease suggest that inhibitors of the EGFR, P13K–Akt, and MAPK pathways should be explored in clinical trials.

MeBC: Squamous Cell Carcinoma Subtype

Pure squamous cell carcinoma (SCC) of the breast is a tumor in which >90% of the malignant cells are of the squamous type [54]. It is considered to represent a subtype of metaplastic carcinoma; however, the management of patients with SCC is often discussed independently from that of MeBC [1, 94], and so it has been included as a separate subentity in this article.

The incidence of SCC of the breast is <0.1% [11–13]. The mean age at presentation is 54–64 years [11, 13, 21, 33, 34]. Patients are exclusively female and the majority are white [11]. Tumors are large, often >4 cm [21, 33], and it is frequently node negative [33]. A review of the literature found that >70% of patients presenting with localized disease had no nodal involvement [21]; however, another series ($n = 33$) found that only 48% of patients had node-negative disease [11]. Up to 10% of patients have metastatic disease at presentation [11, 34]. SCC of the breast is associated with high Ki-67 proliferation in case reports [43, 58]. Over 85% of patients are ER^-PR^- [11, 21, 67] and the majority are also $HER\text{-}2^-$ [11].

Mastectomy is often preferred because of the large tumor size [33]; however, breast-conserving surgery has been employed with varied success [11, 21, 58]. In a series (n=33) from MD Anderson Cancer Center [11], 61% of patients with localized disease at presentation received radiation and 77% received systemic therapy. Twenty-two (71%) patients relapsed. Of the 12 (39%) who experienced locoregional relapse, 40% had breast-conserving surgery and 50% received postoperative radiation, the majority of whom relapsed within the radiation field. Fifty percent of the patients with local recurrence simultaneously relapsed systemically. In addition, disease relapsed locally in two patients while they were receiving adjuvant chemotherapy. There was no significant difference in the recurrence-free survival interval or overall survival time with systemic therapy, a finding in keeping with data from a Spanish series ($n = 11$) [33]. Four patients with ER^+ tumors received tamoxifen. Two of those women were alive at the time of reporting, with a median overall survival duration of 74 months in the ER^+ group.

Both series [11, 33] presented retrospective data, and it is not clear on what basis patients were selected for chemotherapy. In the MD Anderson series [11], five patients were treated with neoadjuvant (anthracycline or taxane based) chemotherapy and none responded; in fact, one patient progressed on therapy. There has been enthusiasm [31] for the use of platinum agents and some success in case reports [58, 95–97]. The MD Anderson series [11] included two patients treated with cisplatin as part of adjuvant chemotherapy for localized disease—one relapsed at 12 months and the other was disease free at 108 months.

Breast SCC is an aggressive disease and the 5-year overall survival rate is poorer than those of other breast cancer histologies [11, 33, 34]. It has been suggested [11, 67] that these tumors resemble basal-like breast cancers—they are usually $ER^-PR^-HER\text{-}2^-$ and highly proliferative, with CK5 or CK6 positivity in 75% of cases, EGFR positivity in 85% of cases, and p63 positivity in 70% of cases [67]. Traditional breast cancer chemotherapy appears to have limited activity [11, 33], and their behavior may be determined by histology rather than the site of disease. Given the squamous histology and the rate of local relapse, earlier initiation of radiation has been suggested; however, frequent relapses within the radiation field raise questions about the radiosensitivity of this tumor [11, 21].

Perhaps a combined chemoradiation approach could be considered for clinical study in breast SCC. Further extrapolating from strategies used for SCC at other sites, it has been suggested that EGFR inhibitors in conjunction with platinums and taxanes be considered [33]. A Japanese group [98] looked at a cell line from a metastatic lymph node of a woman with SCC of the breast to determine the biologic factors driving the aggressive behavior and lack of treatment response. That group found that, after EGFR stimulation, the cells formed protrusions in the cell membrane associated with proteolysis and cell signaling (invadopodia) and developed a fibroblastic morphology, increasing their invasive potential. They suggested that this EGFR-dependent invadopodia formation facilitates invasion, providing a rationale for therapy with EGFR inhibitors [98].

Increased understanding of the molecular drivers of this cancer type and prospective studies are required to advance therapy. The suggestion drawn from these small retrospective studies is that conventional breast cancer chemotherapy and radiation therapy may not enhance outcomes, and perhaps approaches employed for SCC of other sites should be considered.

Papillary Cancer

Papillary breast lesions are a heterogeneous group that includes benign intraductal papillomas, papillomas with atypical ductal hyperplasia or ductal carcinoma in situ (DCIS), papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma, and invasive papillary carcinoma. These can usually be distinguished by cytological features and the distribution of associated myoepithelial cells; however, the wide spectrum of morphology makes pathological interpretation challenging [99, 100]. In addition, the inclusion of mixed histologies in studies confounds interpretation of the data.

This review focuses on encapsulated and solid papillary

carcinomas, which represent ~0.7% of breast cancers [1, 14, 15]. The median age at presentation is 65–70 years [14, 15, 22, 35, 36], and 3.5% of cases are male [22]. The majority (70%) of patients are white [14, 35, 36], followed by black then the Asian race [14]. There is a low frequency of lymph node involvement [63], and ~2.5% of patients have metastatic disease at presentation [14]. These tumors have low proliferative activity [1, 73] and most are ER^+ and PR^+ [35]. In a study by Wynveen et al. [71], all tumors were HER-2^-.

Encapsulated papillary carcinoma is also known as intracystic or encysted papillary carcinoma. It was originally considered an in situ carcinoma; however, myoepithelial cells are usually absent [71] and many now see it as a low-grade invasive carcinoma or part of a spectrum of progression from in situ to invasive disease [101] In addition, metastases to axillary lymph nodes have been reported [102]. However, its associated favorable prognosis suggests that it should be managed as DCIS [14, 100, 22]. Encapsulated papillary carcinomas may be associated with foci of invasive carcinoma located beyond the fibrous capsule, and it is the latter component that is then used for staging purposes.

Solid papillary carcinoma can be considered as a variant of encapsulated papillary carcinoma [63] and also lacks myoepithelial cells within and around the lesion [100], favoring the interpretation that this too represents a low-grade form of invasive carcinoma. However, these tumors also have an indolent course [100]. Pure invasive papillary carcinoma is very rare, controversial, and difficult to diagnose histologically, and it is more likely to be found admixed with breast cancer of another histological subtype [1, 14, 35, 103]. It should not be confused with invasive micropapillary carcinoma, an entirely separate entity that is more common, is more aggressive, and has a different molecular profile.

A number of registry studies provide good demographic and tumor data, but there is limited management information. In a Dutch population study [1], the majority of patients (71%–76%, $n = 1,078$) had surgery alone or surgery and radiation. A minority received unspecified systemic therapy. Wynveen et al. [71] looked at 39 patients with a mix of encapsulated or intracystic papillary carcinoma (IPC), IPC with microinvasion, and IPC with invasive carcinoma. Eleven patients had a mastectomy and 28 had breast-conserving surgery, 14 of whom received radiation. Four patients who had breast-conserving surgery recurred locally, one of whom later developed bone metastasis. No patient received chemotherapy and 10 patients had hormonal therapy; the authors suggested that hormonal therapy should be pursued for this strongly ER^+ disease.

In a study [36] including a mix of pure IPC ($n = 21$), IPC with DCIS ($n = 18$), and IPC with microinvasion ($n = 6$), most patients had breast-conserving surgery. The majority of mastectomies were performed because of positive margins after breast-conserving surgery. All patients with invasive disease had axillary staging, and the majority of patients with invasive disease received adjuvant radiation. Seventy-five percent of patients received adjuvant hormonal therapy. Hormonal therapy was more likely if there was associated microinvasive carcinoma or DCIS. Forty-two of 45 patients were alive at the time of publication [36]. Another study ($n = 40$), again with a mixed population, [15], found that the recurrence and mortality rates were the same in all groups regardless of the type of surgery or the addition of adjuvant radiation. That group reported a disease-specific survival rate of 100% at a median follow-up of 58 months.

Prognosis is better than with IDC, NST [1, 22, 35], with a 5-year survival rate >80% [15, 22, 77]. A population-based registry study, examined >900 cases of IPC; approximately half of the patients had invasive and half had in situ disease. In that study, there was no difference in the survival rate at 10 years [22]. However, classification was based on original pathology reports—the specimens were not reviewed and the criteria used to distinguish between invasive and in situ lesions were not specified, limiting interpretation of these data.

An abstract presented at San Antonio in 2007 [73] reported data on 25,475 tumors tested with the onco*type* DX® breast cancer assay (Genomic Health Inc., Redwood City, CA). Papillary carcinomas of unspecified subhistology represented 0.2% of cases, with a median recurrence score of 7.8 (range, 0–58), significantly lower than that for IDC, consistent with the good prognosis reported elsewhere.

It is difficult to define the optimum management of patients with papillary cancer, given the limited data and heterogeneous populations studied. These are good prognosis cancers, breast-conserving surgery is feasible, and recurrences do occur but they are not frequent and have been managed with local therapy with reasonable outcomes. It is not clear if radiotherapy is beneficial, but it should be considered in the setting of breast-conserving surgery. Adjuvant endocrine therapy is reasonable, but the benefit of systemic chemotherapy is likely to be limited.

Secretory Breast Cancer

This cancer was originally described as juvenile carcinoma and thought to occur exclusively in children [16]. It was subsequently recognized in adults (accounting for two thirds of cases [37, 45, 104]) and renamed secretory carcinoma [44]. It represents 0.15% [16] of all breast cancers and 0.2% of male breast cancers [23]. The median age is 25–40 years [37–39], but it occurs earlier in males, at a median age of 17 years [23]. There are limited data relating to tumor size—the maximum size reported is 16 cm [38] and older patients tend to present with larger tumors [44]. In a review of the literature [37], staging was available in only 24 of 121 cases and six had metastatic disease. Nodal involvement occurs in 20%–30% of cases [23, 24, 39, 75]. Secretory breast cancers demonstrate low Ki67 expression [38, 68], are usually ER^-PR^- [37, 38, 45, 68], and are predominantly HER-2^- [45, 68]. These tumors can resemble acinic cell carcinoma of the salivary gland and stain positively with salivary-type amylase [105]. It is suggested that they share the indolent clinical course and resistance to chemotherapy of these tumors [37].

Ozguroglu et al. [37] reviewed the literature relating to 121 cases, and with surgical data available for 61 patients, only 20% had breast-conserving surgery. There is some controversy about the optimal surgical approach [38]. Local recurrences

occurred in 33% of cases treated with breast-conserving surgery in one series ($n = 12$) [75], and some authors advocate mastectomy [38, 39, 45, 78, 106] with lymph node sampling [16, 38, 45, 107] as the primary surgical approach. Alternatively, it may be possible to consider breast-conserving surgery [23, 37, 45, 107, 108] provided that there are generous margins [23, 45]. Surgery in children poses particular concerns for future breast development [45, 78] and most advocate attempting to preserve the breast bud [38, 39, 78, 106]. However, this may contribute to inadequate surgery and local recurrences [37, 78].

Adjuvant chemotherapy and radiation have been used [37, 38, 78, 107] predominantly in node-positive patients. Some consider that there is insufficient evidence to justify recommending these modalities [23, 37, 78, 107]. However, in adults, others recommend adjuvant radiation following breast-conserving surgery, in line with guidelines for other breast cancer histologies [38, 109]. In children, there are concerns about long-term toxicity and adjuvant radiation is not recommended [39]. Recurrences have been reported in childhood that responded to further local therapy, including radiation [25]. Ozguroglu et al. [37] reported four ($n = 121$) deaths, none of which occurred in childhood; however, two were in patients originally diagnosed as children who relapsed as adults. This group felt that none of the patients who presented during childhood had adequate surgery.

In a review of patients with metastatic disease [45], four cases were identified. Two presented after long disease-free intervals (12 years and 20 years); one of these patients had a rapid deterioration and died shortly after presenting with metastatic disease whereas the other lived for 2 years. The other two patients presented with rapidly disseminating disease; one died within months of presentation but the outcome of the second was not reported. Numerous chemotherapy regimens were employed—5-fluorouracil (5-FU), epirubicin, and cyclophosphamide; vindesine, mitomycin C, and prednisone; doxorubicin and cyclophosphamide; and docetaxel, cisplatin, and infusional 5-FU—without reported success. One patient lived for 1 year off therapy after progressing through three lines of chemotherapy [45].

Secretory breast cancer has a long natural history [23, 37] and is associated with a good prognosis [23, 37, 78]. There is often a long interval to relapse [16, 45]. Risk factors for late recurrences are not clear [37], but most of the metastatic cases reported had positive axillary nodes and sentinel node sampling should thus be considered, including in children [16, 37]. Large tumor size, older age, infiltrative margins [23, 78], and breast-conserving surgery [106] have also been implicated in recurrence risk.

Secretory breast cancers are low-grade triple-negative ($ER^-PR^-HER\text{-}2^-$) cancers that express basal cell markers [104, 107]. However, they are genetically unique and are associated with a better prognosis than other basal-like tumors [107]. Tognon et al. [110] reported that secretory breast cancers demonstrate a balanced chromosomal translocation t(12;15)(p13;q25), which causes fusion of the ETS variant gene 6 (*ETV6*) and the neurotrophic tyrosine kinase receptor 3 (*NTRK3*). *ETV6–NTRK3* fusion activates the Ras–MAPK and PI3K–Akt pathways, promoting breast cell proliferation and survival [107]. This translocation results in the expression of a functional tyrosine kinase that has potent transforming activity and may be a primary genetic lesion in secretory breast cancer [107].

This is a rare tumor, but it does account for most of the breast cancers described in childhood. It is associated with a good prognosis, but local recurrence can be an issue. The roles of adjuvant chemotherapy and radiation are unclear. Whereas the *ETV6–NTRK3* fusion gene has been described in patients with localized disease, data are lacking in the metastatic setting. However, given the poor responses to multiple chemotherapeutic agents, tyrosine kinase and Ras inhibitors could be considered for clinical trials.

Conclusion

Each of the tumor subtypes described herein represents a small but real cohort of patients with breast cancer. Unfortunately, the data are heterogeneous and incomplete. We have attempted to amalgamate the information available, to provide an overview of how each subgroup behaves and responds to therapy. Emerging molecular data provide us with the opportunity to better understand the underlying biology and suggest potential treatment strategies for study. However, we are mindful of the paucity of data, and the management of each patient must be considered in the context of their unique clinical presentation, correlated with the evidence-based principles that apply to more common breast cancer histologies.

Author Contributions

Manuscript writing: Karen A. Cadoo, Orla McArdle, Anne-Marie O'Shea, Colm P. Power, Bryan T. Hennessy
Final approval of manuscript: Karen A. Cadoo, Bryan T. Hennessy

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